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The main objective of this project is to evaluate the effects of soy phytoestrogen consumption on reproductive hormones and prostate tissue markers of cell proliferation and androgen action in men at high risk of prostate cancer. The hypothesis is that alteration of endogenous hormones is a mechanism by which soy phytoestrogens prevent prostate cancer. A randomized parallel arm study will be performed, in which 90 men at high risk of prostate cancer will be randomized to receive one of three dietary supplements for six months: 1) soy powder containing phytoestrogens; 2) phytoestrogen-free soy powder; or 3) phytoestrogen-free milk powder. Urine and blood will be collected at 0, 3 and 6 months, for evaluation of prostate cancer risk factors, including serum hormones (testosterone, dihydrotestosterone, androstenedione, dehydroepiandrosterone, estradiol, estrone, 3α, 17β-androstanediol glucuronide, sex hormone binding globulin) and prostate specific antigen, as well as urinary estrogen and phytoestrogen metabolites. Before and after the intervention, prostate biops will be performed to evaluate prostate tissue expression of apoptosis (TUNEL assay, Bax, Bcl-2), proliferation (Ki67, PCNA and androgen receptor density. At this point, 10 subjects have completed the feeding study, 17 subjects are enrolled, and biological samples have been collected, processed and stored.

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INTRODUCTION

The low risk of prostate cancer in Asia is thought to be due to dietary factors, including soy consumption. Studies showing an inverse association between prostate cancer risk and urinary excretion of soy phytoestrogens suggest that phytoestrogens contribute to the cancer-preventive effects of soy. One mechanism by which soy phytoestrogens are thought to be cancer-preventive is *via* reduction of endogenous sex hormones known to stimulate prostate cell growth. Despite the interest in soy phytoestrogens for prevention of prostate cancer, there have been no studies in men to evaluate the effects of soy phytoestrogen consumption on sex steroids and prostate tissue biomarkers, and no studies evaluating effects of phytoestrogen metabolism on sex steroids in men.

The main objective of this project is to evaluate the effects of soy phytoestrogen consumption on reproductive hormones and prostate tissue markers of cell proliferation and androgen action in men at high risk of prostate cancer. The underlying hypothesis is that alteration of endogenous hormones is a mechanism by which soy phytoestrogens prevent prostate cancer.

The specific aims of this study are to compare the effects of consumption of phytoestrogen-containing soy protein, phytoestrogen-free soy protein, and milk protein, on risk factors for prostate cancer (endogenous hormones, prostate specific antigen, prostate tissue markers of cell proliferation and hormone action), in men at high risk for prostate cancer. Comparing the three groups will enable us to distinguish the specific effects of soy phytoestrogens from effects caused by other soy components. A randomized parallel arm study will be performed, in which 90 men at high risk of prostate cancer will be randomized to receive one of three dietary supplements for six months: 1) soy powder containing 1 mg phytoestrogens/kg body weight; 2) phytoestrogen-free soy powder; and 3) phytoestrogen-free milk powder. Urine and blood will be collected at 0, 3 and 6 months, for evaluation of serum hormones (testosterone, dihydrotestosterone, androstenedione, dehydroepiandrosterone, estradiol, estrone, 3α, 17β-androstanediol glucuronide, sex hormone binding globulin) and prostate specific antigen, as well as urinary estrogen and phytoestrogen metabolites. Before and after the intervention, prostate biopsies will be performed to evaluate prostate tissue expression of apoptosis (TUNEL assay, Bax, Bcl-2), proliferation (Ki67, PCNA), and androgen receptor density.

Data from *in vitro*, animal and epidemiological studies suggest that androgens and estrogens play a role in prostate carcinogenesis. Soy phytoestrogens have been shown to alter sex steroids in women in a potentially beneficial direction, yet such studies in men have not been reported. Studies of the hormonal effects of soy phytoestrogens in men will contribute to our knowledge of the cancer-preventive mechanisms of soy phytoestrogens, and may lead to dietary recommendations for prevention of prostate cancer.

BODY

According to the original statement of work, the following tasks were to be performed during the first two years of this project:

Task 1: Hire and train staff, coordinate with Veteran's Administration and Fairview-University Hospital staff, establish all study protocols

Task 2: Perform feeding study on 60 men

- Recruit 60 men at high risk of prostate cancer and randomize into three intervention groups: phytoestrogen-containing soy protein, phytoestrogen-free soy protein, or milk protein
- Perform feeding study; process and store serum, urine and biopsy slides
- Analyze samples: serum hormones and SHBG by RIA; serum free and total PSA by ELISA; urine estrogen metabolites and phytoestrogens by GC-MS; biopsy slides by immunohistochemistry

Although the grant officially began on April 15, 2002, final approval from the DOD IRB was not received until January 2003. As a result, we were not able to begin recruiting subjects until February 2003.

From February-April 2003, six subjects began the feeding study. From May 2003-April 2004, 30 subjects were enrolled in the study. Of these 36 subjects, 9 withdrew (25%) for the following reasons:

- Consumption of excess alcohol
- Type II diabetic on weight loss program
- Difficulty with time commitment
- Unwillingness to drive to study site from out of town home
- Gastrointestinal problems with powder (2 on milk powder, 1 on soy powder)
- Dislike of powder taste
- Difficulty remembering to take powder
- Concern about weight gain

As of May 2004, 10 subjects have completed the study and 17 are enrolled. We are a little more than one year behind in progress. This is not surprising given the late start due to the time required for DOD IRB approval.

Clearly we did not anticipate the difficulty we would face in recruiting and retaining subjects. The main cause has been reduced PSA screening, which has resulted in far fewer biopsies, and a much slower recruiting rate than initially planned. We also did not anticipate the 25% dropout rate.

In order to increase subject recruitment and retention, we have done the following:

- increased the age range to 50-85 yrs
- provided travel reimbursements for subjects who live out of town
- included subjects who had negative biopsies within the past 2 yr (as opposed to the past 6 mo as originally planned)
- increased flexibility in setting appointments

As a result of these changes, we have doubled subject accrual from 2 subjects/mo in 2003 to 4 subjects/mo in 2004. If we continue accruing subjects at a rate of 4/mo, and

the dropout rate continues at 25%, we will accrue 36 subjects in the next year and 12 subjects in the extension year, for a total of 75 subjects.

In order to achieve our goal of 90 subjects, and given that it may be difficult to keep up a rate of 4 subjects/mo, particularly in the winter months when many retired Minnesotans travel to warmer climates, we propose to widen the inclusionary criteria by

- including subjects with prostate cancer who are undergoing "watchful waiting"
- allowing the subjects to miss their 3 mo appointment
- extending the study to 7 mo for subjects who travel from Minnesota
- shipping the soy protein powder to the winter home as necessary
- remaining persistent in communication despite the distance
- being as flexible as possible with appointments

Finally, we are in the process of adding the University of Minnesota Hospital as a second recruitment site. Up until this point, we have recruited all subjects from the VA Medical Center in Minneapolis.

We are also hoping to increase enrollment by three additional mechanisms that will require additional funding. The first is to include patients whose PSA is sufficiently high to recommend an initial biopsy, but who might not require a second biopsy. For these patients, we would have to pay for the second biopsy and provide compensation to the subjects as well. Second, we would like to provide compensation to all subjects for participation. Third, we hope to add two community sites for recruitment (Park Nicollet Health Services and Metro Urology). To fund these additional mechanisms, we have applied to the DOD for additional funding through the IDEA Award program ("Dietary Phytoestrogens and Prostate Cancer Prevention: Phase 2" PC041141).

Tissue analyses are set to begin June 2004. Urinary and blood analyses will begin as soon as 30 subjects have completed the study, by October 2004.

KEY RESEARCH ACCOMPLISHMENTS

- Enrollment of 36 subjects, completion of 10 subjects
- Collection, processing and storage of tissue, blood, and urine samples
- Improvement of the recruitment strategies to double enrollment in the last four months

REPORTABLE OUTCOMES

None at this time

CONCLUSIONS

The human feeding study has successfully begun and biological samples have been processed and are being stored as stated in the study design. At this point there are no reportable data from which to draw conclusions.

REFERENCES

None

APPENDICES

None